**Citation:**

Kanis JA, Johansson H, Oden A, De Laet C, Johnell O, Eisman JA, Mc Closkey E, Mellstrom D, Pols H, Reeve J, Silman A, Tenenhouse A. A meta-analysis of milk intake and fracture risk: Low utility for case finding. *Osteoporos Int.* 2005; 16 (7): 799-804.

**PubMed ID:** 15502959

**Study Design:**

Meta-analysis

**Class:**

M - Click here for explanation of classification scheme.

**Research Design and Implementation Rating:**

POSITIVE: See Research Design and Implementation Criteria Checklist below.

**Research Purpose:**

To quantify the fracture risk associated with a low dietary intake of calcium as judged by self-reported intake of milk in an international setting and to explore the dependence of this risk with age, sex and bone mineral density (BMD).

**Inclusion Criteria:**

Six prospectively studied cohorts drawn randomly from populations in Europe, Australia and Canada were used for the meta-analysis:

- The European Vertebral Osteoporosis Study (EVOS/EPOS)
- Canadian Multicentre Osteoporosis Study (CaMos)
- Dubbo Osteoporosis Epidemiology Study (DOES)
- The Rotterdam Study
- The Sheffield Study and a cohort from Gothenburg study.

**Exclusion Criteria:**

None stated.

**Description of Study Protocol:**

**Recruitment**

Data were collected from six prospectively studied cohorts.

**Design**

Meta-analysis study.

**Dietary Intake/Dietary Assessment Methodology**

- The construct of the question to determine intake of milk differed between the cohorts studied. Where glasses of milk were recorded (EVOS/EPOS, CaMos, Sheffield, Gothenburg), an intake of less than one glass of milk a day was taken as the level to dichotomise the intake of milk (approximately 250mg calcium daily or less). The size of glass was not standardized. The choice of cut-off was pragmatic, but corresponds to the intake below which a large case control study indicated a significant increase in hip fracture risk

- In the case of Rotterdam and DOES, total calcium intake was recorded by a food frequency questionnaire (FFQ). A threshold of more than 500mg of calcium was used in these cohorts to dichotomize the variable on the assumption that approximately 50% of calcium intake is in the form of milk in these countries. Where intake was recorded at different ages of life, they utilized current intake of milk.

**Statistical Analysis**

- The risk of fracture was estimated by Poisson regression applied to each cohort and each sex separately
- Covariates included current time, current age, milk intake and milk intake times current age
- Since risk assessment with clinical risk factors may be undertaken with or without the use of BMD, an additional model included the covariates above with bone mineral density
- Bone mineral density was undertaken at the femoral neck by DXA with the exception of the Gothenburg cohort, which measured bone mineral density at the distal forearm using the DTX-200 Osteometer
- The beta coefficients of each cohort for each sex were weighted according to the variance and merged to determine the weighted mean and standard deviation (SD)
- The risk ratio of those on low calcium intakes versus those on higher calcium intakes was equal to $e^{mean}$
- Heterogeneity was tested by the $I^2$ statistic. There was no significant heterogeneity between cohorts ($P>0.3$; $I^2=13$; 95% confidence interval=0% to 54% for osteoporotic fracture and $I^2=0$, 0% to 25% for hip fracture), and a fixed effects model was used.

**Data Collection Summary:**

**Dependent Variables**

- Variable 1, Risk of Fracture: Prospective fracture ascertainment was undertaken by self-report (Sheffield, EVOS/EPOS), and verified from hospital central databases (EVOS/EPOS, CaMos, DOES, Rotterdam, Sheffield and Gothenburg II). Fractures considered to be due to osteoporosis were analyzed and in addition, hip fracture alone was considered separately. An osteoporotic fracture was one considered to be due to osteoporosis by the investigator.
- For the EVOS study osteoporotic fractures comprised hip, forearm, humeral or clinical spine fractures
- For the CaMos study, they comprised fractures of the spine, pelvis, ribs, distal forearm, forearm and hip
- In the other cohorts (Sheffield, Rotterdam, Gothenburg, DOES) fractures at sites considered to be characteristic for osteoporosis were extracted which, in addition to the sites above, included fractures of the proximal humerus, other femoral fractures, clavicle, scapula and tibial fractures in women.

**Independent Variables**

- Cohort
- Sex
- Milk Intake:
    - Where glasses of milk were recorded (EVOS/EPOS, CaMos, Sheffield, Gothenburg), an intake of less than one glass of milk a day was taken as the level to dichotomize the intake of milk (approximately 250mg calcium daily or less). The size of glass was not standardized. The choice of cut-off was pragmatic but corresponds to the intake below, which a large case control study indicated a significant increase in hip fracture risk [30].
    - In the case of Rotterdam and DOES, total calcium intake was recorded by a food frequency questionnaire. A threshold of less than 500mg of calcium was used in these cohorts to dichotomize the variable on the assumption that approximately 50% of calcium intake is in the form of milk in these countries [31,32]. Where intake was recorded at different ages of life, they utilized current intake of milk.

**Control Variables**

- Current time
- Current age
- Milk intake
- Milk intake times current age
- Bone mineral density.

**Description of Actual Data Sample:**

- *Initial N:* 39,563
- *Attrition:* 39,563
- *Mean age:* In years between the studies (21 to 103 years)
- *Ethnicity:* Unclear but likely European, Canadian and Australian
- *Location:* Europe, Australia, Canada.

**Table 1: Details of Cohorts Studied**

| Cohort | Sample Size | Person-years | Mean Age (Years) | Age Range (Years) | Percent Female | Low Calcium Intake (%) | Any Fracture | Osteoporotic Fracture | Hip Fracture |
|---|---|---|---|---|---|---|---|---|---|
| EVOS/EPOS | 13,445 | 40,388 | 63.8 | 41–91 | 52 | 60 | 720 | 720 | 45 |
| CaMos | 9,401 | 26,656 | 62.1 | 25–103 | 69 | 37 | 586 | 316 | 42 |
| DOES | 2,065 | 15,920 | 70.4 | 57–95 | 61 | 40 | 516 | 405 | 104 |
| Rotterdam | 5,408 | 32,447 | 67.7 | 55–94 | 59 | 3 | 636 | 473 | 130 |
| Sheffield | 2,173 | 6,901 | 80.0 | 74–96 | 100 | 16 | 292 | 243 | 63 |
| Gothenburg II | 7,071 | 29,645 | 58.9 | 21–89 | 100 | 14 | 441 | 312 | 29 |
| Total | 39,563 | 151,957 | 64.3 | 21–103 | 69 | 35 | 3,191 | 2,469 | 413 |

**Summary of Results:**

- Low intake of calcium, as judged by the intake of milk, does not confer a substantial increase in fracture risk
- No significant association was noted between intake of milk and the risk of hip fracture at any age and in either sex. For osteoporotic fractures (but not for hip fracture alone), a small, but significant risk was found from the age of 80 years, but not in younger individuals. The association was no longer significant when adjusted for BMD.
- There was a weak but significant correlation between intake of milk and BMD ($R=0.03643$, $P=4.5 \times 10^{-10}$).

**Table 2: Risk Ratio of Fracture Associated with Low Milk Intake in Men and Women (risk ratio not adjusted for BMD)**

| Outcome | Sex | RR | 95% CI |
|---|---|---|---|
| Osteoporotic fracture | M | 1.11 | 0.90–1.36 |
| | F | 1.09 | 0.98–1.22 |
| Hip fracture | M | 1.50 | 0.89–2.54 |
| | F | 1.09 | 0.82–1.44 |

**Table 3: Risk Ratio (RR) for Osteoporotic Fracture and 95% CI in Men and Women Combined with a Low Milk Intake vs. the Remainder of the Population**

| Age (years) | RR without BMD | | RR with BMD | |
|---|---|---|---|---|
| | Mean | 95% CI | Mean | 95% CI |
| 50 | 0.97 | 0.79–1.19 | 0.96 | 0.76–1.22 |
| 55 | 0.99 | 0.84–1.16 | 0.98 | 0.82–1.18 |
| 60 | 1.00 | 0.88–1.13 | 0.98 | 0.85–1.14 |
| 65 | 1.01 | 0.91–1.13 | 1.00 | 0.88–1.15 |
| 70 | 1.05 | 0.95–1.18 | 1.05 | 0.92–1.20 |
| 75 | 1.11 | 0.99–1.24 | 1.09 | 0.96–1.25 |
| 80 | 1.15 | 1.02–1.30 | 1.12 | 0.98–1.28 |
| 85 | 1.18 | 1.01–1.37 | 1.14 | 0.97–1.35 |
| All ages | 1.10 | 1.00–1.21 | 1.06 | 0.95–1.19 |

**Table 4: Risk Ratio (RR) for Hip Fracture and 95% Confidence Interval Comparing Men and Women Combined with a Low Milk Intake vs. the Remainder of the Population**

| Age (years) | RR without BMD | | RR with BMD | |
|---|---|---|---|---|
| | Mean | 95% CI | Mean | 95% CI |
| 50 | 1.53 | 0.61–3.83 | 1.29 | 0.44–3.76 |
| 55 | 1.47 | 0.70–3.12 | 1.29 | 0.54–3.06 |
| 60 | 1.41 | 0.78–2.55 | 1.26 | 0.64–2.48 |
| 65 | 1.34 | 0.84–2.14 | 1.20 | 0.70–2.07 |
| 70 | 1.25 | 0.85–1.84 | 1.14 | 0.72–1.80 |
| 75 | 1.16 | 0.84–1.60 | 1.08 | 0.74–1.58 |
| 80 | 1.13 | 0.85–1.50 | 1.08 | 0.79–1.49 |
| 85 | 1.11 | 0.81–1.52 | 1.10 | 0.78–1.55 |
| All ages | 1.17 | 0.91–1.50 | 1.10 | 0.83–1.47 |

**Author Conclusion:**

- The principal finding of the present study undertaken in large and internationally drawn cohorts is that a low intake of calcium, as judged by the intake of milk, does not confer a substantial increase in fracture risk
- If habitual dietary intake of calcium was a significant risk factor for fractures, a simple questionnaire on the intake of milk would be unlikely to be of value as an adjunct to case finding.

***Reviewer Comments:***

*The authors noted the following limitations for the study:*

- *The construct of the question concerning calcium intake differed somewhat between cohorts and at best lacks precision and accuracy. Although total calcium intake was recorded in two of the studies and would have included calcium supplements, in other cohorts calcium supplements may have confounded the relationship between intake of milk and total intake of calcium. The effect of this heterogeneity is likely to weaken any association.*
- *They were unable, using the construct of the question, to examine intakes of calcium lower than 500mg daily, so that they could not exclude a threshold effect as has been shown in case control studies for hip fracture risk, albeit with a threshold similar to the one that we used to dichotomize milk intake.*
- *They neglected sources of calcium intake other than milk, including cheese and yoghurt, and variations in dietary vitamin D or sunlight exposure. This study should not, therefore, be misinterpreted as suggesting no causative role of calcium in the causation of fractures, nor a role for calcium nutrition in their prevention. Indeed, the association of an increased risk of osteoporotic fracture in the elderly is consistent with an important role for calcium in the elderly in whom other risk factors are more prevalent, including immobility and lack of sunlight exposure.*
- *The use of more accurate but more complex instruments to determine intake is likely to be unfeasible in a general practice setting.*

---

***Research Design and Implementation Criteria Checklist: Review Articles***

| **Relevance Questions** | | |
|---|---|---|
| 1. | Will the answer if true, have a direct bearing on the health of patients? | Yes |
| 2. | Is the outcome or topic something that patients/clients/population groups would care about? | Yes |
| 3. | Is the problem addressed in the review one that is relevant to nutrition or dietetics practice? | Yes |
| 4. | Will the information, if true, require a change in practice? | No |

| **Validity Questions** | | |
|---|---|---|
| 1. | Was the question for the review clearly focused and appropriate? | Yes |
| 2. | Was the search strategy used to locate relevant studies comprehensive? Were the databases searched and the search termsused described? | Yes |
| 3. | Were explicit methods used to select studies to include in the review? Were inclusion/exclusion criteria specified and appropriate? Were selection methods unbiased? | Yes |
| 4. | Was there an appraisal of the quality and validity of studies included in the review? Were appraisal methods specified, appropriate, and reproducible? | Yes |
| 5. | Were specific treatments/interventions/exposures described? Were treatments similar enough to be combined? | Yes |
| 6. | Was the outcome of interest clearly indicated? Were other potential harms and benefits considered? | Yes |
| 7. | Were processes for data abstraction, synthesis, and analysis described? Were they applied consistently across studies and groups? Was there appropriate use of qualitative and/or quantitative synthesis? Was variation in findings among studies analyzed? Were heterogeneity issued considered? If data from studies were aggregated for meta-analysis, was the procedure described? | Yes |
| 8. | Are the results clearly presented in narrative and/or quantitative terms? If summary statistics are used, are levels of significance and/or confidence intervals included? | Yes |
| 9. | Are conclusions supported by results with biases and limitations taken into consideration? Are limitations of the review identified and discussed? | Yes |

| | | |
|---|---|---|
| 10. | Was bias due to the review's funding or sponsorship unlikely? | Yes |